REMARKS

Claims 1–21, 23–25, 28–30, 33, 35–37, 40–50, 52–54, 107, 252–253, and 258–262 are pending in the application and stand rejected. Claims 1, 17–21, 23, 54, 107, and 259–261 have been amended. Claims 273 and 274 have been added. No new matter has been introduced. Reconsideration and allowance of Claims 1–21, 23–25, 28–30, 33, 35–37, 40–50, 52–54, 107, 252–253, 258–262, and 273–274 is respectfully requested.

The Rejection of Claims 259–261 Under 35 U.S.C. § 112, Second Paragraph

Claims 259–261 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. The Examiner has taken the position that Claims 259–261 are indefinite because all variables in the claims are not defined. The Examiner acknowledges that the variables $\gamma 1$ and $\gamma 2$ are defined. However, the Examiner has taken the position that the variables ε and σ are not adequately defined. In order to clarify the invention, Claims 259–261 have been amended to recite in relevant part:

$$\begin{pmatrix} \varepsilon_1 \\ \varepsilon_2 \end{pmatrix} \text{ is distributed as a bivariate normal random variable with mean } \begin{pmatrix} 0 \\ 0 \end{pmatrix}$$

$$\text{and covariance matrix } \begin{pmatrix} \sigma_1^2 & \sigma_1\sigma_2 \\ \sigma_2\sigma_1 & \sigma_2^2 \end{pmatrix};$$

Support for this amendment is found in the specification, published as WO 2004/013727, at page 93, line 23, to page 24, line 21. Removal of this ground of rejection is respectfully requested.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

The Rejection of Claims 1, 2, 5–11, 42–44, 49, 50, 52, 53, 252, and 258 Under 35 U.S.C. § 102(b) as Being Anticipated by Aitman et al., *Nature Genetics 21*:76–83 (1999)

Claims 1, 2, 5–11, 42–44, 49, 50, 52, 53, 252, and 258 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Aitman et al., *Nature Genetics 21*:76–83 (1999). The Examiner characterizes Aitman et al. as disclosing a method of genetically analyzing complex disorders, such as diabetes, by correlating a QTL for different traits of diabetes (insulin-mediated glucoase uptake and catecholamine-mediated lipolysis) with mapping of the expression trait for the gene Cd36. The Examiner notes that Aitman et al. discloses mapping using a plurality of rat/hamster radiation hybrid cell lines to test a plurality of chromosomal locations for linkage to Cd36. Applicants respectfully traverse this ground of rejection for at least the following reasons.

While not acquiescing to the Examiner's position, but in order to facilitate prosecution, Claim 1, from which Claims 2, 5–11, 42–44, 49–50, 52–53, 252, and 258 depend, has been amended to recite at step (A):

> (A) identifying an expression quantitative trait loci (eQTL) for said gene **G** using a first quantitative trait loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for said gene **G** as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for said gene **G** in an organism in said plurality of organisms, and wherein said first QTL analysis comprises (1) testing for linkages between the plurality of expression statistics for said gene **G** and a plurality of locations along a at least one chromosome of the plurality of organisms, comprising (i) testing for a linkage between (a) the genotypes of said plurality of organisms at a position in the chromosome of said species and (b) said

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

plurality of expression statistics for said gene **G**; (ii) advancing the position in the chromosome by an amount; and (iii) repeating steps (i) and (ii) until the end of the chromosome is reached or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for said gene **G** using allelic association analysis . . . .

Support for this amendment is found in the specification as filed, published as WO 2004/013727; for example, at page 21, line 6, to page 23, line 32, and original Claim 17.

It is noted that Claim 1, as amended, is not anticipated by Aitman et al. because the cited reference does not teach every element of the claimed invention. For example, it is noted that Aitman et al. does not teach testing for linkages between a plurality of expression statistics for gene G and a plurality of locations along a chromosome of the plurality of organisms, and repeating the analysis until the end of the chromosome is reached, as required by Claim 1, as amended. Accordingly, removal of this ground of rejection is respectfully requested.

The Rejection of Claims 1 and 12–16 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Aitman et al.

Claims 1 and 12–16 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Aitman et al. Applicants traverse this ground of rejection for at least the following reasons.

Claim 1 has been amended at step A as indicated *supra*. Aitman et al. does not teach, suggest, or provide any motivation to practice the claimed invention, as amended.

Obviousness is determined by analyzing the factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). *KSR* confirmed that the *Graham* factor analyses should be used in determining whether a claimed invention is obvious under 35 U.S.C. § 103(a).

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

KSR Int'l v. Teleflex Inc., 127 S. Ct. 1727, 1734 (2007). The inquiry under *Graham* includes ascertaining the differences between the prior art and the claims at issue.

The Differences Between Aitman et al. and the Claimed Invention, as Amended

It is noted that Aitman et al. does not teach or suggest the identification of an expression quantitative trait loci (eQTL), as claimed. As described in the instant specification at page 7, lines 20–24, an expression trait loci (eQTL) is identified using a plurality of expression statistics for a gene G, where each expression statistic in the plurality of expression statistics represents an expression value for gene G in an organism in a plurality of organisms. As recited in Claim 1, as amended, the method comprises:

> (A) identifying an expression quantitative trait loci (eQTL) for said gene **G** using a first quantitative trait loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for said gene **G** as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for said gene **G** in an organism in said plurality of organisms, and wherein said first QTL analysis comprises (1) testing for linkages between the plurality of expression statistics for said gene **G** and a plurality of locations along at least one chromosome of the plurality of organisms, comprising (i) testing for a linkage between (a) the genotypes of said plurality of organisms at a position in the chromosome of said species and (b) said plurality of expression statistics for said gene **G**; (ii) advancing the position in the chromosome by an amount; and (iii) repeating steps (i) and (ii) until the end of the chromosome is reached or (2) comparing genotype data from

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

each organism in the plurality of organisms to the plurality of expression statistics for said gene **G** using allelic association analysis . . . .

It is noted that the differential expression experiments described in Aitman et al. did not identify a quantitative trait loci (QTL), much less an expression quantitative trait loci (eQTL), by testing for linkages between a plurality of expression statistics for gene G and a plurality of locations along a chromosome of the plurality of organisms, and repeating the analysis until the end of the chromosome is reached, as required by Claim 1, as amended. In contrast to the claimed invention, the only differential expression analysis described in Aitman et al. involved analysis of the gene Cd36, namely, the comparison of hybridization signals between the SHR strain and insulin-sensitive control (BN and SHR.4 strains), resulting in the identification of three clones encoding rat Cd36 that showed reduced hybridization signals for SHR as compared to those of BN and SHR.4.

The Differences Between the Teachings of Aitman et al. and Claim 1 Are Not Obvious Differences

As noted above, Aitman et al. does not teach or suggest the identification of an expression quantitative trait loci (eQTL) wherein said analysis comprises testing for linkages between a plurality of expression statistics for gene G and a plurality of locations along at least one chromosome of the plurality of organisms, and repeating the analysis until the end of the chromosome is reached, as required by Claim 1, as amended. Rather, in contrast to the claimed invention, the only differential expression analysis described in Aitman et al. involved the comparison of hybridization signals between the SHR strain and insulin-sensitive control strains, resulting in the identification of clones encoding rat Cd36.

Accordingly, applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness because the cited reference does not teach or suggest all the elements

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

of the claimed invention, as amended. Accordingly, removal of this ground of rejection is respectfully requested.

The Rejection of Claims 1, 3, 4, 17–21, 23–25, 28–30, 33, 35–37, 40, 41, and 45–49 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Aitman et al. in View of Dominiczak et al., *Hypertension 35*(2):164–172 (2000)

Claims 1, 3, 4, 17–21, 23–25, 28–30, 33, 35–37, 40, 41, and 45–49 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Aitman et al. in view of Dominiczak et al., *Hypertension 35*(2):164–172 (2000). The Examiner characterizes Aitman et al. as discussed *supra*. The Examiner further acknowledges that Aitman et al. does not show mapping of a QTL with a precision of 1cM, or analysis of a human QTL. The Examiner further acknowledges that Aitman et al. does not show analysis of a trait affected by a plurality of mutations in different genes, or a high frequency of disease causing alleles, or non-Mendelian inheritance (limited penetrance) of a trait, or a trait that is hypertension. The Examiner cites Dominiczak et al. et al., *Hypertension 35*(2):165–172 (2002), as disclosing that human genes have been identified that contribute to hypertension with a lod score of greater than 2, and concludes that it would have been obvious to a person of ordinary skill in the art at the time the invention was made to modify the analysis of Aitman et al. by analyzing human QTL markers. Applicants traverse this ground of rejection for at least the following reasons.

It is noted that Claim 1, from which Claims 3, 4, 17–21, 23–30, 33, 35–37, 40–41, and 45–49 depend has been amended as described *supra*.

It is further noted that Claim 17 has been amended and now recites:

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

The method of claim 1, wherein said first QTL analysis comprises repeating steps (i) and (ii) of Step (A) until all chromosomes of said species have been tested.

Support for this amendment is found in the specification at page 21, line 6, to page 23, line 32.

Claims 18–21 and 23 have been amended to depend from Claim 1. No new matter has been introduced.

Claims 1, 3, 4, 17–21, 23–25, 28–30, 33, 35–37, 40, 41, and 45–49 are believed to be patentable over Aitman et al. in view of Dominiczak et al. for at least the following reasons. As noted above, Aitman et al. does not teach or suggest the identification of an expression quantitative trait loci (eQTL) as claimed. For example, Aitman et al. does not teach or suggest testing for linkages between a plurality of expression statistics for gene G and a plurality of locations along at least one chromosome of the plurality of organisms, and repeating the analysis until the end of the chromosome is reached, as required by Claim 1, as amended.

The teachings of Dominiczak do not cure the deficiencies of Aitman et al. Dominiczak discloses the identification of clinical quantitative trait loci (cQTL) for hypertension using blood pressure subphenotypes and cardiovascular complications, such as left ventricular hypertrophy, kidney failure, and stroke. Dominiczak does not disclose, teach, suggest, or provide a reason to perform an eQTL analysis that uses a plurality of expression statistics for gene G as a quantitative trait. The QTL described by Dominiczak are cQTL because the blood pressure and cardiovascular phenotypes are phenotypic values for clinical traits T in an organism in a plurality of organisms rather than expression values for a gene G in organisms in a plurality of organisms.

Moreover, Dominiczak does not teach or suggest identifying an expression quantitative trait loci (eQTL) for a gene using a QTL analysis comprising testing for linkages between a

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

plurality of expression statistics for gene G and a plurality of locations along at least one chromosome of the plurality of organisms, and repeating the analysis until the end of the chromosome is reached, as required by Claim 1, as amended.

Accordingly, applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness because even if the cited references were to be combined, the cited references do not teach or suggest all the elements of the claimed invention, as amended. Accordingly, removal of this ground of rejection is respectfully requested.

The Rejection of Claims 54, 107, 253, and 262 Under 35 U.S.C. § 103(a) as Being Unpatentable Over Aitman et al. in View of Manly et al., *Mammalian Genome 10*:327–334 (1999)

Claims 54, 107, 253, and 262 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Aitman et al. in view of Manly et al., *Mammalian Genome 10*:327–334 (1999). The Examiner characterizes Aitman et al. as discussed *supra*. The Examiner further notes that Aitman et al. discloses the use of a computer program termed MAPMAKER, however the Examiner acknowledges that Aitman et al. does not provide details of their genetic mapping calculations. The Examiner cites Manly et al. as disclosing the use of computer software for QTL analysis. The Examiner notes that Manly et al. discloses that two methods widely used are least squares regression and maximum likelihood estimation, as well as the use of interval mapping. The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to use a computer running the MAPMAKER program as disclosed in Aitman et al. because Manly et al. shows that MAPMAKER as well as other programs are useful to map QTL markers. Applicants traverse this ground of rejection for at least the following reasons.

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS^{PLLC}
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

Like Claim 1, from which Claims 253 and 262 depend, it is noted that independent Claims 54 and 107 have been amended at step (A) and now recite:

> (A) identifying an expression quantitative trait loci (eQTL) for said gene **G** using a first quantitative trait loci (QTL) analysis, wherein said first QTL analysis uses a plurality of expression statistics for said gene **G** as a quantitative trait, wherein each expression statistic in said plurality of expression statistics represents an expression value for said gene **G** in an organism in said plurality of organisms, and wherein said first QTL analysis comprises (1) testing for linkages between the plurality of expression statistics for said gene **G** and a plurality of locations along at least one chromosome of the plurality of organisms, comprising (i) testing for a linkage between (a) the genotypes of said plurality of organisms at a position in the chromosome of said species and (b) said plurality of expression statistics for said gene **G**; (ii) advancing the position in the chromosome by an amount; and (iii) repeating steps (i) and (ii) until the end of the chromosome is reached or (2) comparing genotype data from each organism in the plurality of organisms to the plurality of expression statistics for said gene **G** using allelic association analysis . . . .

Support for this amendment is found in the specification as filed, published as WO 2004/013727, for example, at page 21, line 6, to page 23, line 32; and page 88, line 27, to page 90, line 31.

It is submitted that Claims 54 and 107 are each patentable over Aitman et al. for at least the same reasons that Claim 1 is patentable over Aitman et al. For example, as discussed above, Aitman et al. does not teach or suggest the identification of an expression quantitative trait loci

LAW OFFICES OF
CHRISTENSEN O'CONNOR JOHNSON KINDNESS PLLC
1420 Fifth Avenue
Suite 2800
Seattle, Washington 98101
206.682.8100

(eQTL) as claimed. As described in the instant specification at page 7, lines 20–24, an expression trait loci (eQTL) is identified using a plurality of expression statistics for a gene G, where each expression statistic in the plurality of expression statistics represents an expression value for gene G in an organism in a plurality of organisms. It is further noted that Aitman et al. does not teach or suggest testing for linkages between a plurality of expression statistics for gene G and a plurality of locations along a chromosome of the plurality of organisms, and repeating the linkage analysis until the end of the chromosome is reached, as required by Claims 1, 54, and 107, as amended.

The teachings of Manly et al. do not cure the deficiencies of Aitman et al. Manly et al. does not disclose the identification of an expression quantitative trait loci (eQTL). It is further noted that Manly et al. does not teach or suggest identifying an expression quantitative trait loci (eQTL) for a gene using a QTL analysis comprising testing for linkages between a plurality of expression statistics for gene G and a plurality of locations along at least one chromosome of the plurality of organisms, and repeating the analysis until the end of the chromosome is reached, as required by Claim 1, as amended.

Accordingly, applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness because even if the cited references were to be combined, the cited references do not teach or suggest all the elements of Claims 54 and 107, as amended. Accordingly, removal of this ground of rejection is respectfully requested.

New Claims

Claims 273 and 274 have been added. No new matter has been introduced.

Independent Claim 273 is directed to a method for associating a gene G in the genome of a species with a clinical trait T exhibited by one or more organisms in a plurality of organisms of

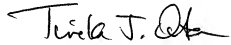
said species, comprising step A, which is identical to step A recited in original Claim 1. Support for Step B is found in the specification as filed; for example, at page 21, line 6, to page 23, line 32.

Conclusion

Applicants believe that the pending claims are in condition for allowance. Reconsideration and allowance are respectfully requested. The Examiner is further requested to contact applicants' representative at 206.695.1655 to discuss any issues that may facilitate prosecution of this application

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS^{PLLC}



Tineka J. Quinton
Registration No. 53,496
Direct Dial No. 206.695.1655

TJQ:jlg